

has fewer than 4 rotatable bonds, or has no more than one sulfur, phosphorous or halogen atom.

A⁵ 44. (amended once) The method of claim 30 wherein said target molecule is RNA and said baseline affinity expressed as a dissociation constant is about 50 millimolar.

REMARKS

Claims 1-120 remain pending in this application. Claims 30, 31, 34, 35, 40, and 44 have been amended. Support for the amendments can be found throughout the specification and in the original claims. No new matter has been introduced.

I. Objections to the Claims

Claims 30 and 37 are objected to for having alleged typographical errors. These claims have been amended according to the suggestions of the Office Action. Accordingly, Applicants respectfully request withdrawal of the objections to the claims.

II. The Claims are Enabled

Claims 30-46 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly containing non-enabled subject matter. Applicants traverse the rejection because the claims are well-enabled.

It is well established that the test for enablement is whether undue experimentation would be required to practice the claimed invention. *See, e.g., In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Contrary to the assertions of the Office Action, one skilled in the art would not need to carry out undue experimentation to practice the claimed subject matter. In fact, the reasons provided in the Office Action supporting alleged non-enablement appear to be based on misunderstanding of the invention. For example, the Office Action erroneously assumes that both standard and test compounds are required to bind at the same site in the target molecule. There is no such requirement, and it is unclear to Applicants how such

assumptions could be attributed to the claimed subject material. The specification does not set forth that standard and test compounds need to bind at the same site in a target molecule, nor is there any requirement that there be any particular knowledge of where either molecule binds. Thus, the non-enablement rejection is baseless.

In view of the apparent misunderstanding, the Office Action incorrectly concludes that one skilled in the art would be required to engage in undue experimentation to determine what standard molecules can be used with a particular target molecule. Indeed, one skilled in the art would find it sufficient to know 1) whether or not the standard compound binds to a target, and often, 2) the approximate affinity with which the standard binds. The specification, for example, on page 34, line 1 to page 35, line 22, clearly sets forth suitable examples of standards and targets and provides ample guidance for selection of standards according to the invention. For example, standards for RNA and DNA targets can include ammonium, primary amines, secondary amines, etc. Standards for proteins can include formate, acetate, propionate, phosphates, borates, etc. The specification also provides suitable standard-target binding affinities, which typically range, for example, from about the order of nanomolar to about 100 millimolar (expressed as the dissociation constant). Since knowledge of these characteristics are sufficient for the skilled artisan to select an appropriate standard for a particular target molecule, no undue experimentation is required.

Due to the Office Action's misunderstanding of the claimed subject material, and the inappropriate assumption that standard and target are required to bind at the same site in the target molecule, the rejection of the claims for non-enablement is without merit. As fully set forth above, no undue experimentation would be necessary to select a standard compound to practice the invention, and thus, the claims are well-enabled by the specification. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of the claims under 35 U.S.C. § 112, first paragraph.

III. Rejections under 35 U.S.C. § 112, second paragraph

Claim 30 stands rejected under 35 U.S.C. § 112, second paragraph, as allegedly being incomplete for omitting essential structural cooperative relationships of elements. Applicants traverse the rejection because no such omission was made.

As discussed above, the Office Action appears to misunderstand the claimed subject matter, and as such, the rejection is without merit. For example, the Office Action makes the *incorrect* statement that the standard compound “must bind to the same site on a target molecule as those members of a group of compounds...” (page 5, ¶4). Since, as already discussed, same-site binding of standard and test compounds is not a part of the invention, the claim does not omit any essential matter. Therefore, the claims clearly set forth the subject matter Applicants regard as the invention.

Claims 30, 33, 34, 35, 40 and 45 stand rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite. Applicants traverse the rejection because the claims are clear and definite within the patent laws.

The Office Action mistakenly asserts that the phrases “baseline affinity” and “background noise” are unclear in claim 30. Since these terms are well-defined in the specification (see, *e.g.*, page 12, lines 16-21), and/or one skilled in the art would understand the meaning of these phrases, Applicants believe the claim is clear and definite. In order to even more clearly recite the claimed material, however, claim 30 has been amended. Accordingly, the rejection is rendered moot.

The claims are further rejected over the allegedly unclear terms of “diverse” and “related.” The Office Action mistakenly concludes that the claims are indefinite since these terms are terms of degree, and the specification allegedly does not provide a standard for determining degree. However, just because a claim includes a term of degree does not automatically render the claim indefinite. *Seattle Box Co., v. Industrial Crating & Packing, Inc.*, 731 F.2d 818, 221 U.S.P.Q. 568 (Fed. Cir. 1984). Acceptability of the claim language depends on whether one of ordinary skill in the art would understand what is claimed, in light of the specification. (*See*, M.P.E.P. § 2173.05(b)) Applicant submits that these terms do not render the claims indefinite, and one skilled in the art would have no difficulty in determining the metes and bounds of the claims that

contained such terms. For example, further defining just HOW diverse or HOW related the recited compounds are would not serve to enhance clarity of the claims because such limitations are inconsequential to understanding the claimed subject matter. In other words, any degree of diversity or relatedness is suitable for the invention, and one skilled in the art would understand this in light of the specification. Thus, the claims are clear and definite.

Claim 34 is rejected over the allegedly unclear phrase “historical repository of compounds.” This phrase, however, is well defined in the specification at, for example, page 32, lines 4-11 and refers to a collection of all compounds made by an entity, such as, for example, a university or pharmaceutical company. Thus, this term does not render the claim indefinite, and the metes and bounds of the claim can be readily discerned by one skilled in the art.

The Office Action alleges that claim 40 is unclear. Applicants submit that the claim as originally written is clear and definite. The claim, however, has been amended to even more clearly recite the claimed subject matter.

The Office Action further alleges that claim 45 is not clear because of the recitation of “ammonium.” Ammonium is a defined chemical entity that is common knowledge to the art-skilled. According to *Webster's New College Dictionary*, 1999, the definition for ammonium is “[t]he chemical ion NH_4^+ .” Thus, contrary to what is asserted in the Office Action, there would be no confusion over the meaning of ammonium.

In view of the above discussion, Applicants submit that the claims set forth the subject matter regarded as the invention, and the metes and bounds of the claims are well defined. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of the claims under 35 U.S.C. § 112, second paragraph.

IV. The Claims are Not Obvious

The Cheng, Lim, and Loo references

Claims 30-46 stand rejected under 35 U.S.C. § 103(a) over Cheng, *et al.*, *J. Am. Chem. Soc.* **1995**, *117*, 8859 (hereinafter “Cheng”), Lim, *et al.*, *J. Mass Spectrometry*

1995, 30, 708 (hereinafter "Lim"), and Loo, *Mass Spectrometry Reviews*, 1997, 16, 1 (hereinafter "Loo"). Applicants traverse the rejection because *prima facie* obviousness is not established.

To establish *prima facie* obviousness, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974). The references cited in the Office Action collectively fail to teach all the elements of the claimed subject material. For example, no cited reference teaches a *standard compound that forms a non-covalent binding complex with a target molecule*. The Office Action appears to incorrectly suggest that the ammonium acetate in solutions of antibiotic and/or peptide ligands of Lim serves as a standard compound. However, it would have been apparent to the skilled artisan that ammonium acetate was not used in the capacity of a standard compound, but instead, used as a buffer to stabilize solution pH.¹ Moreover, the ammonium acetate is not reported to form a non-covalent binding complex with any of the antibiotics or peptide ligands reported therein, and thus, ammonium acetate cannot be considered to be a standard compound. Since Lim fails to teach a standard compound, the reference is inappropriately relied upon as such.

The references also fail to teach numerous other elements of the claimed subject material. Some of the claim elements that are not taught include 1) mixing a standard compound with excess target compound, 2) acquisition of mass spectral signals for unbound target and target complexed with standard in the same mixture for adjusting the mass spectrometer to achieve certain signal strengths in a certain ratio, 3) adding test compounds to a test mixture of standard and target, and numerous other elements. Since the references fail to describe these and other characteristics of the claimed subject matter, *prima facie* obviousness cannot be established.

In addition, obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *In re Fine*, 837 F.2d

¹ See, e.g., Lim, page 709, first line under header Sample Preparation, which reports the preparation of stock solutions in 5 mM ammonium acetate *buffer* (pH 7).

the target, would only be redundant and serve no purpose since the ligands employed in the experiments of Cheng were already *known* binders with *known* affinities (pg. 8859, sentence spanning cols. 1 and 2). In this regard, there would have been no motivation to include a standard compound in the methods of Cheng. Thus, the claims are not obvious.

The Office Action further appears to incorrectly assert that comparing known and unknown ligands for the screening of lead molecules for drug discovery would have provided motivation to include a standard compound in the methods of Cheng. Contrary to the assertions of the Office Action, there is no such motivation because, as discussed above, the group of ligands analyzed in the reference were *known* ligands with *known* binding affinities. Addition of a standard, that by definition has known binding affinity, would not allow a comparison of known and unknown ligands since there is no unknown ligand. As such, screening by comparing unknown and known ligands would not have motivated one skilled in the art to modify the methods of Cheng to include a standard compound.

In addition, even if the methods of Cheng were modified to include a standard compound, the claimed subject matter would not be produced. The addition of a standard compound certainly does not imply that any of the following steps of the claims would also be carried out: 1) mixing an amount of standard with an excess amount of target, 2) adjusting the operating performance conditions of a mass spectrometer to achieve a certain signal strength for standard complexed with target relative to unbound target, 3) introducing a group of compounds into a test mixture of target and standard, to name just a few. Accordingly, the proposed modification to the methods of the Cheng reference does not produce the claimed subject matter.

Applicants submit that the combination of references proposed in the Office Action is improper for numerous reasons, only some of which are discussed above. Since the Office Action fails to point to legally sufficient motivation in the cited references, and the references themselves do not collectively teach all the elements of the claimed invention, *prima facie* obviousness has not been established. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of the claims under 35 U.S.C. § 103(a).

V. Restriction Requirement

Applicants hereby request reconsideration of the restriction requirement imposed in the previous Office Action dated April 10, 2001. It is respectfully requested that claims 1-26 and 47-56 (Groups I, III, and IV) be examined collectively with elected claims 30-46. Applicants submit that the presently elected claims (claims 30-46) are sufficiently related to the proposed additional claims such that it would not be a serious burden on the Examiner to conduct a search on the encompassed subject matter. Claims 1-56 are clearly related in that they are directed to mass spectrometric methods for the selection of compounds that have affinity for a target molecule. Accordingly, examination of claims 1-56 should not pose a serious burden to the Examiner.


VI. Drawings

Applicants acknowledge receipt of the "Attachment for PTO-948" outlining changes for prosecution of applications containing drawings. Formal drawings have been filed on date even herewith under separate cover to the Draftsperson.

In view of the foregoing, Applicant submits that the claims as amended are in condition for allowance, and an early Office Action to that effect is earnestly solicited.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version with markings to show changes made.**"

Respectfully submitted,


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**VERSION WITH MARKINGS TO SHOW CHANGES MADE****In the Specification:**

Please replace the section under the heading FIELD OF THE INVENTION on page 1 of the specification with the following replacement section.

The present invention is related to mass spectrometry methods for detecting binding interactions of ligands to substrates and in particular to methods for determining the mode of binding interaction of [legends] ligands to substrates.

In the Claims:

Please amend claims 30, 31, 34, 35, 40, and 44 as follows.

30. (amended once) A method of selecting those members of a group of compounds that can form a non-covalent complex with a target molecule [and where the affinity of the members for the target molecule is greater than a baseline affinity] comprising:

selecting a mass spectrometer;

selecting a standard compound that forms a non-covalent binding complex with said target molecule, said non-covalent binding complex having a baseline affinity;

mixing an amount of said standard compound with an excess amount of said target molecule such that unbound target molecule is present in said mixture;

introducing said mixture of said standard compound and said target molecule into said mass spectrometer;

adjusting the operating performance conditions of said mass spectrometer such that the signal strength of said standard compound bound to said target molecule is from 1% to about 30% of signal strength of unbound target molecule;

introducing a sub-set of said group of compounds into a test mixture of said target molecule and said standard compound;

introducing said test mixture into said mass spectrometer;

identifying the members of said sub-set that form complexes with said target [with an affinity *greater* than said baseline] by discerning [those] signals arising from

said members complexed with said target [that have a signal strength greater than the background noise of said mass spectrometer] and identifying the [member] members by their respective molecular [mass] masses.

31. (amended once) The method of claim 30 wherein said [signal is] signals are measured as the relative ion abundance.

34. (amended once) The method of claim 33 wherein said collection library of diverse compounds comprises a historical repository of compounds, a collection of natural products, a collection of drug substances, a [collections] collection of intermediates produced in forming drug substances, a collection of dye stuffs, a commercial collection of chemical substances or a combinatorial library of related compounds.

35. (amended once) The method of claim 33 wherein said collection library of diverse compounds comprises a library of compounds having from 2 to about 100,000 members.

40. (amended once) The method of claim 30 wherein each of the members of said group of compounds, independently, has a molecular mass less than about 200 Daltons, has fewer than 4 rotatable bonds, or has [or] no more than one sulfur, phosphorous or halogen atom.

44. (amended once) The method of claim 30 wherein said target molecule is RNA and said [preset] baseline affinity expressed as a dissociation constant is about 50 millimolar.